REMARKS

Claims 1-3, 5-8,10-11, and 13-26 remain pending in the above identified application, with claims 21-26 standing ready for further action on the merits, and claims 1-3,5-8, 10-11 and 13-20 standing withdrawn from further consideration on the merits based on an earlier restriction requirement of the Examiner.

Enclosed 37 CFR § 1.132 Declaration

Enclosed herewith is a 37 CFR § 1.132 declaration of Dr. Nomura, which is pertinent to a consideration of the patentability of the instant invention as claimed. The Examiner is respectfully requested to review Dr. Nomura's enclosed Declaration at this time, as it is material to a consideration of the patentability of the pending claims under consideration at present. The enclosed Declaration is the second 37 CFR § 1.132 declaration of Dr. Nomura that has been filed in the matter of this case.

A copy of Mr. Nomura's enclosed 37 CFR § 1.132 Declaration was previously filed in the USPTO on April 6, 2005, with applicant's prior reply, but was apparently either *(i)* not scanned into the electronic file wrapper of this application at the USPTO by way of an error on the part of the USPTO, and/or *(ii)* not scanned into the electronic file wrapper of this application at the USPTO as being an alleged *artifact* sheet that could not be scanned (*see electronic image file wrapper - items filed April 6, 2005*).

In any event, a copy of Mr. Nomura's second declaration (originally filed April 6, 2005) is enclosed herewith based on the following comments contained in the Examiner's Advisory Action of June 20, 2005 *(see page 5 thereof)*:

> To address Applicant's comments regarding the Declaration of Dr. Nomura, no second declaration has been received. There is nothing on the record to show that the oil-in-water emulsion of the prior art is not the same as the claimed oil-in-water emulsion.

Accordingly, a new copy of Mr. Nomura's second 37 CFR 1.132 Declaration is enclosed herewith for the Examiner's review.

Also enclosed is a copy of Berton Zbar, et al. "Tumor Suppression by Cell Walls of *Mycobacterium bovis* Attached to Oil Droplets", J Nat Cancer Inst 48: 831-835, 1972. A copy of this document was also enclosed with the prior response of April 6, 2005 (and was apparently properly scanned into the electronic file wrapper at the USPTO (*see 5 page document dated 04/06/2005*)), but is included herewith for completeness and to ensure that the Examiner considers the same.

Still further, also enclosed herewith is a copy of the stamped postcard that accompanied the reply of April 6, 2005, clearly indicating that a copy of Mr. Nomura's 37 CFR § 1.132 declaration and the Berton Zbar, et al. publication was enclosed with the filed reply.

Incorporation By Reference

Remarks set forth in the prior reply of April 6, 2005 at page 11, line 1 to page 15, last line are incorporated herein by reference in their entirety. The Examiner is respectfully requested to review the same remarks at this time in combination with the attached 37 CFR § 1.132 declaration of Mr. Nomura, and the attached Berton Zbar, et al. publication.

It is submitted that upon review of the earlier submitted remarks filed on April 6, 2005, in combination with the enclosed 37 CFR § 1.132 Declaration of Mr. Nomura, and the attached Berton Zbar, et al. publication, the Examiner will fully understand that each of the pending claims under consideration at present (i.e., claims 21-26) are fully patentable under all provisions of Title 35 of the United States Code.

CONCLUSION

Based on the remarks presented herein, as well as the submission of Dr. Nomura's enclosed second declaration, it is submitted that each of the pending claims under consideration is allowable at present. Accordingly, the Examiner is respectfully requested to issue a notice of allowance at present indicating the allowability of each of pending claims 21-26.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
John W. Bailey, #32,881

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

JWB:enm
0020-4802P

Attachment(s):

Copy of Date Stamped Postcard filed with prior Reply in the USPTO on April 6, 2005;

37 CFR § 1.132 Declaration of Dr. Nomura (Second Declaration of Mr. Nomura); and

Berton Zbar, et al. "Tumor Suppression by Cell Walls of *Mycobacterium bovis* Attached to Oil Droplets", J Nat Cancer Inst 48: 831-835, 1972.

Papers Filed herewith on: April 6, 2005 37

DOCKET NO.: 0020-4802P ATTY.: JWB

APPLICANT(S): Azuma et al.

APPLN. NO: 09/743,750 FILED: Jan. 16, 2001

PAT NO.:

- ☐ New Application with Transmittal Letter
- ☐ Utility ☐ Design ☐ CIP ☐ PCT ☐ Provisional
- ☐ Filing Under 37 CFR 1.53(b) ☐ CONT ☐ DIV
- ☐ Filing Under 37 CFR 1.114(RCE)
- ☐ Specification Consisting of: _____ pages
- ☐ Combined Declaration & Power of Attorney
- ☐ Assignment / Cover Letter
- ☐ Letter to Official Draftsman
- ☐ Drawings ___ Sheets ☐ Formal ☐ Informal ☐ Red-Ink
- ☐ Completion of Filing Requirements, PCT/DO/EO/905 or Formalities Letter and Executed Declaration
- ☐ Priority Document(s) / Cover Letter, No. Doc. _____
- ☒ Amendment: 37 CFR 1.116
  - ☒ Transmtl Ltr ☒ Large Entity ☐ Small Entity
- ☐ Response _____
- ☐ Information Discl Stmnt. PTO-1449(s) _____ doc(s)
  - ☐ PTO / ISA / 210
- ☒ Notice of Appeal ☐ Appeal Brief
- ☐ Issue Fee Transmittal ☐ Sequence Listing
- ☒ FEES: $1520.00 (Ck#9034708)
- ☐ Letter:
- ☒ Other: 37 CFR 1.132 Dec. of Dr. Nomura; Zbar et al. Reference

DOCKET NO. 0020-4802P

Receipt is hereby acknowledged of the papers filed as indicated in connection with the above identified case.
COMMISSIONER OF PATENTS AND TRADEMARKS
Due Date: April 6, 2005
Handcarry: _____

IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICANT: Ichiro Azuma, et al.

SERIAL NO: 09/743,750 GROUP: 1645

FILED: January 16, 2001 EXAMINER: Vanessa L. Ford

FOR: FORMULATIONS USEFUL FOR IMMUNOTHERAPY FOR CANCERS CONTAINING BACTERIAL COMPONENT AS AN ACTIVE INGREDIENT

DECLARATION UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Takehiko Nomura, a citizen of Japan and residing at Osaka, Japan, say and declare as follows:

1. I received the degree of Ph. Dr. from Kyoto University in Japan in 1998.

2. I have been working at Sumitomo Pharmaceuticals Research Center since 1998, studying pharmaceutical science and drug formulation.

3. I am a member of Parenteral Formulation Research Group in Formulation Research Laboratories.

4. I am an author or co-author of 3 * papers related to pharmaceutical science and cancer gene therapy:

*) Pharm Res. 1998 Jan;15(1):128-32;
J Control Release. 1998 Mar 31;52(3):239-52; and
Cancer Res. 1997 Jul 1;57(13):2681-6.

5. Although I am not one of the inventors in U.S. Serial Number 09/743,750, I am very familiar with the subject matter thereof and have been researching the subject matter thereof since 1998.

6. I have conducted the following experiments related to the subject matter of the 09/743,750 application.

7. Experiments

In order to demonstrate that the properties of an oil-in-water emulsion prepared using an organic solvent are different from those of an emulsion prepared not using an organic solvent, the following experiments were conducted.

MATERIALS AND METHODS

The emulsions comprising BCG-CWS and an oil were prepared according to the procedures described in the specification of the present application, U.S. Patent Application No. 09/743,750.

Experiment 1

Preparation using CLEARMIX®

1) Compositions

Composition of the emulsion with an organic solvent

Ingredients	contents	Units
BCG-CWS	146.5	mg
Squalane	3.8	g
Polysorbate 80 (HM)	2.4	g
Heptane	9	mL
Ethanol (99.5) Highest grade reagent	1	mL
Distilled water for injection	Totally 240	g

Composition of the emulsion without an organic solvent

Ingredients	contents	Units
BCG-CWS	146.5	mg
Squalane	3.8	g
Polysorbate 80 (HM)	2.4	g
Distilled water for injection	Totally 240	g

2) Emulsification conditions

Device: CLEARMIX^{R} (Mtechnique Inc.)

Procedures: A mixture of BCG-CWS and an oil in 0.02% Polysorbate 80 was stirred at 16,000 rpm for 5 minutes to conduct the emulsification, and then 10 % Polysorbate 80 was added thereto, and the emulsion was stirred at 4,600rpm for 1 minute.

Experiment 2

Preparation using Potter type homogenizer

1) Composition

BCG-CWS: 0.6mg/mL, Squalane: 0.8 w/w%, Polysorbate 80: 1 %

Scale: 5ml

BCG-CWS: 3 mg, Squalane: 50μL

Organic solvent: 10%EtOH/90%Heptane : 2mL

2) Emulsification conditions

Device: Potter type homogenizer (luchi Inc.)

Procedures: The emulsification was conducted at 2,000 rpm for 3 minutes using the device.

OBSERVATIONS

1) Visual examination with a microscopy

2) Comparisons of segregation rate and appearances after the segregation

RESULTS

1) Visual examination with a microscopy

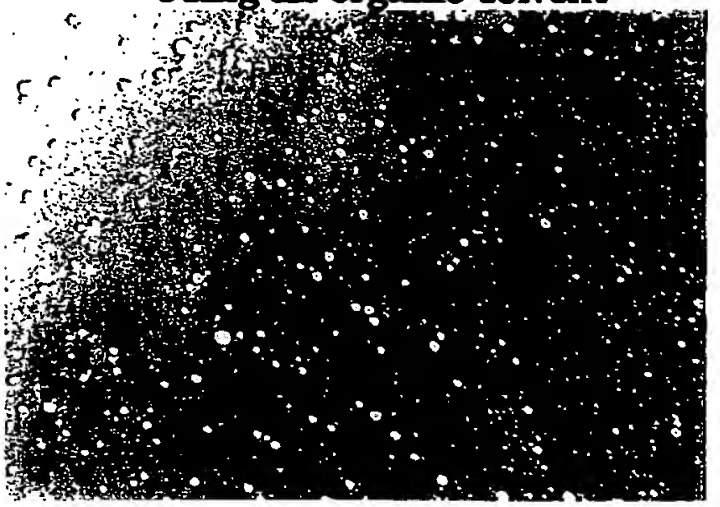
Experiment 1

Preparation using CLEARMIX^R

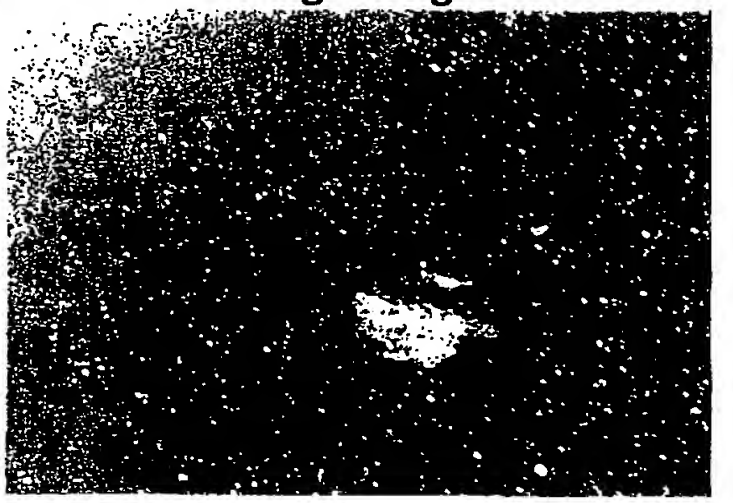
Photomicrographs of the emulsions just after the emulsification obtained by Experiment 1 are shown in the following:

Fig. 1: Comparison of the appearances of the emulsions obtained with CLEARMIX^R

Using an organic solvent



Not using an organic solvent



The emulsion obtained not using an organic solvent was found to contain the BCG-CWS mass that were sharply distinguished from emulsion particles.

Experiment 2

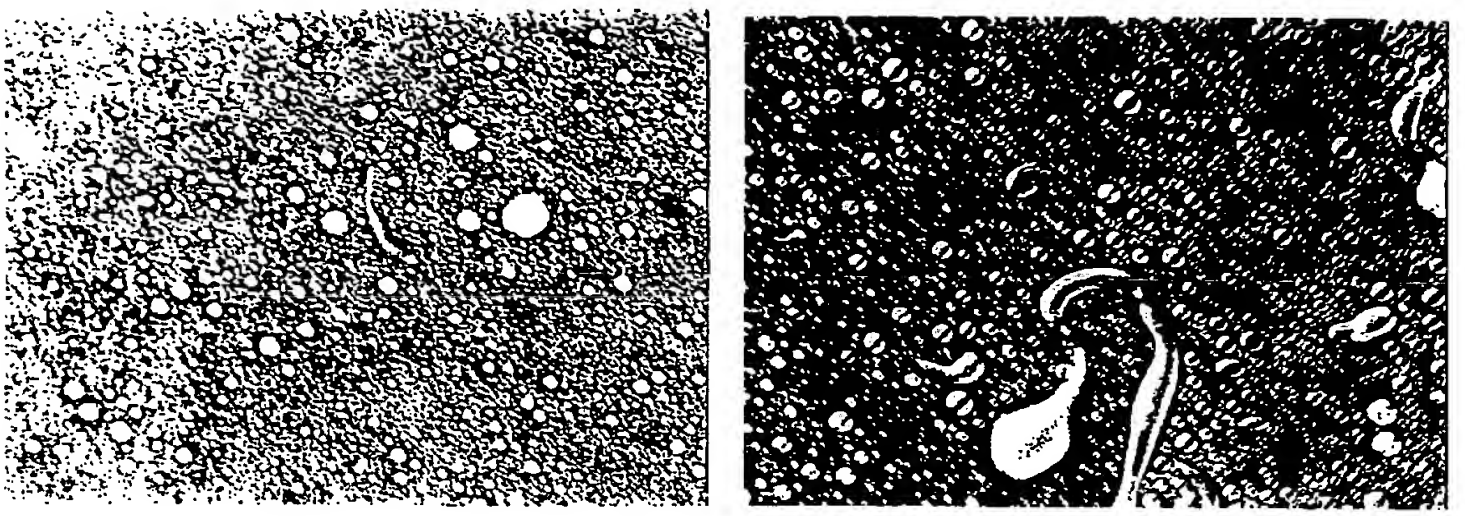
Preparation using Potter type homogenizer

In a similar manner, the appearances of the emulsions obtained with Potter type homogenizer, which was weaker in the emulsification power than CLEARMIX^R, were compared.

Fig. 2: Comparison of the appearances of the emulsions obtained with Potter type homogenizer

Using an organic solvent

Not using an organic solvent

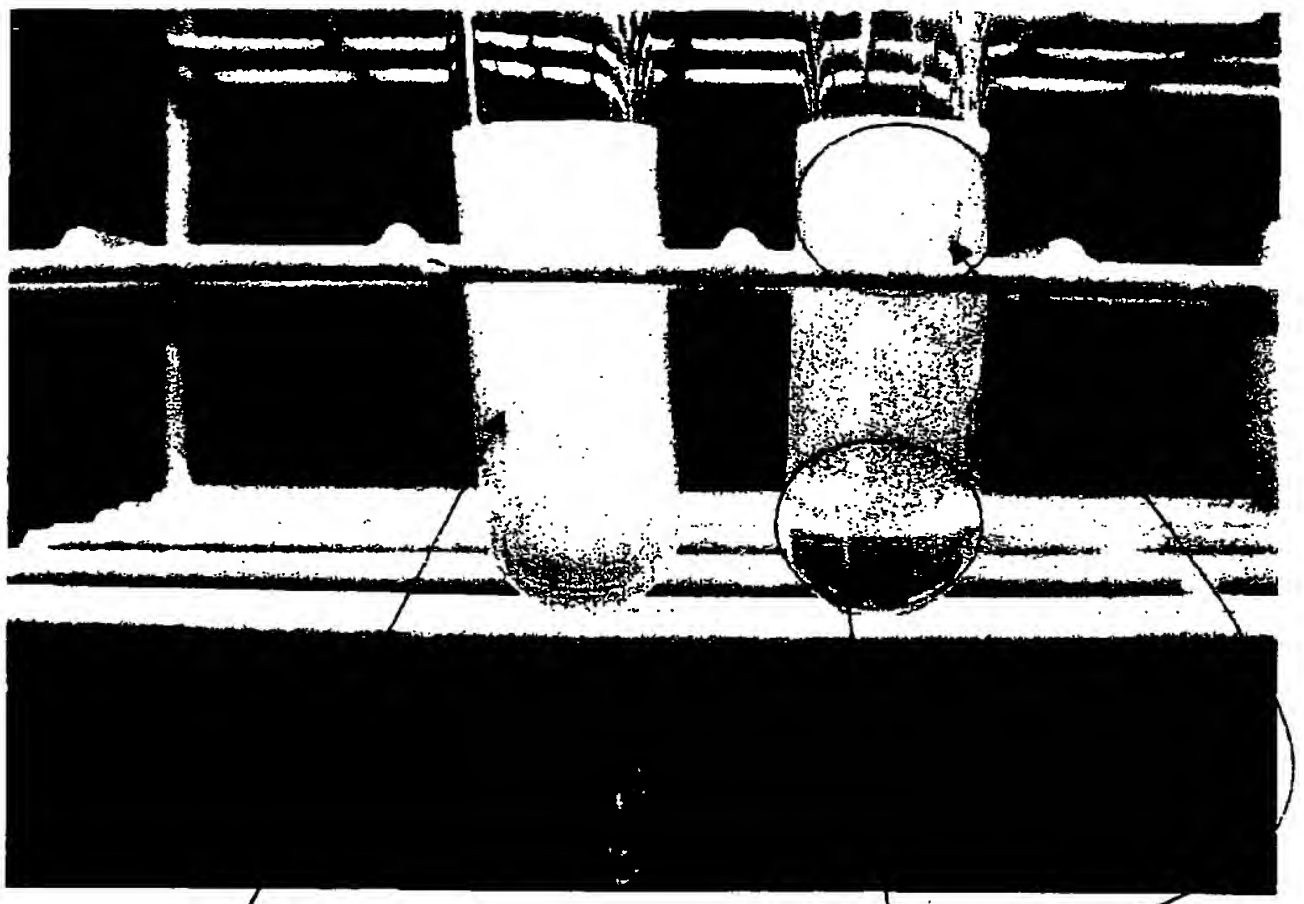


The emulsion obtained not using an organic solvent just after the emulsification was found to contain the amorphous large mass.

2) Emulsion stability

The emulsions obtained in Experiment 2 were left for a period of time, and compared in the conditions.

Fig. 3: Comparison of the appearances of the emulsions obtained with Potter type homogenizer, left for about 24 hours



Using an organic solvent

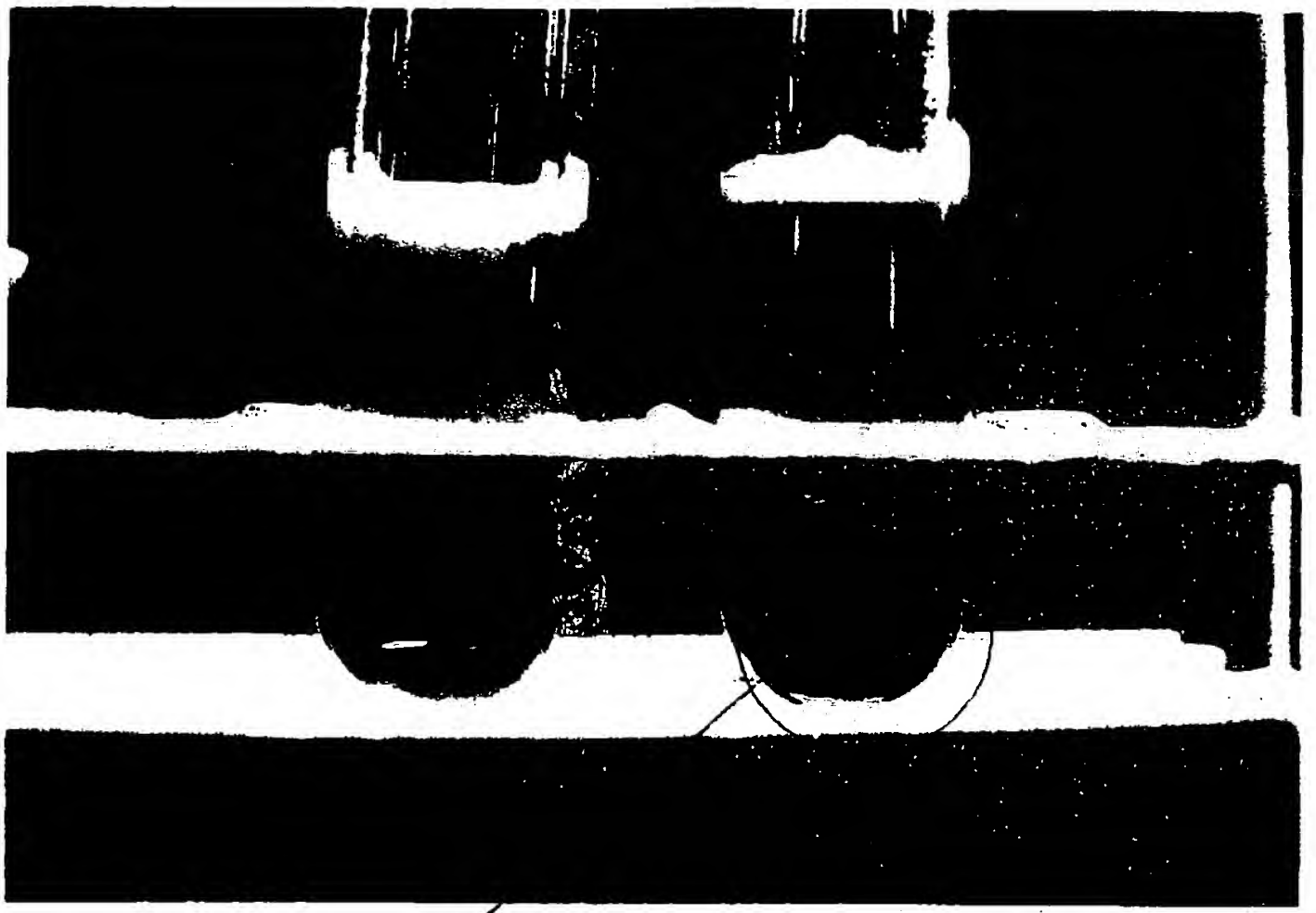
Not using an organic solvent

The degrees of transparency between the upper phase and the lower phase are different, showing that the segregation rate is fast.

The emulsion obtained not using an organic solvent was found to segregate gradually (the lower phase become transparent), showing that the emulsion obtained using an organic solvent is more stable than that not sing an organic solvent.

Then, the same emulsions were further left for one month to examine the long-term stability.

Fig. 4: Comparison of the appearances of the emulsions obtained with Potter type homogenizer, left for one month



Left: Using an organic solvent Right: Not using an organic solvent

Insoluble aggregation, in which BCG-CWS that is not covered with the oil was

segregated.

The emulsion obtained not using an organic solvent was found to contain the segregated insoluble mass, which is believed to be produced by the segregation of the BCG-CWS that had not been covered with the oil from the time point when the emulsion was prepared, which segregation lasted during a period of one month. If the BCG-CWS was covered with the oil, it was impossible that the BCG-CWS was released into the aqueous phase from the oil droplets since BCG-CWS is insoluble in water.

This finding shows that an emulsion as prepared varies depending on the presence or the absence of an organic solvent during the preparation.

8. The undersigned declares further that all statement made herein of his own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that Such willful false statement may jeopardize the validity of above identified application or any patent issuing thereon.

30 March 2005
Date

Takehiko Nomura
Dr. Takehiko Nomura

Brief Communication

Tumor Suppression by Cell Walls of *Mycobacterium bovis* Attached to Oil Droplets [1]

Beton Zbar, Herbert J. Rapp, *and* Edgar E. Ribi,[2] *Biology Branch, National Cancer Institute,[3] Bethesda, Maryland 20014*

SUMMARY—The growth of syngeneic guinea-pig tumor transplants in skin was suppressed if the tumor cells were inoculated together with bacillus Calmette-Guérin (BCG) cell walls attached to oil droplets. Tumor growth was not inhibited if the tumor cells were given together with 1) BCG cell walls, 2) oil droplets, and 3) oil droplets and BCG cell walls prepared so as to prevent attachment of the walls to the oil droplets. Animals in which tumor growth was suppressed acquired systemic tumor immunity.—J Nat Cancer Inst 48: 831–835, 1972.

WE HAVE reported that the intradermal growth of a transplantable, syngeneic guinea-pig hepatocarcinoma in normal guinea pigs is suppressed if the tumor cells are inoculated together with living bacillus Calmette-Guérin (BCG) (*1*, *2*). Heat-killed BCG or extracts of tubercle bacilli did not inhibit tumor growth. For treatment of cancer patients, however, nonliving mycobacterial preparations with tumor-suppressive properties would be preferable to living BCG. We now report that cell walls of BCG attached to oil droplets possess potent tumor-suppressive activity. Preparations of this type are as effective as living BCG in preventing pulmonary tuberculosis in mice and monkeys (*3*, *4*).

MATERIALS AND METHODS

Animals.—Sewall-Wright inbred strain-2 male guinea pigs were obtained from the Laboratory Aids Branch, Division of Research Services, National Institutes of Health (*5*). Skin grafts between members of the strain are not rejected (*6*). Guinea pigs were grouped 6 per cage and fed Wayne guinea pig chow daily and kale 3 times a week.

Tumors.—We have described the induction of primary hepatomas in strain-2 guinea pigs fed the water-soluble carcinogen diethylnitrosamine (*7*) and the antigenic and biologic properties of the transplantable tumors derived from the primary hepatomas (*8*, *9*). A transplantable hepatoma designated tumor line 10 (seventh to eleventh transplant generations) was used. Tumor line 10 is a hepatocellular carcinoma converted to ascites form. Intradermal inoculation of 10^5 ascites line-10 tumor cells leads to progressive intradermal growth and metastases to the regional lymph nodes. Animals

[1] Received November 16, 1971; accepted January 3, 1972.

[2] Rocky Mountain Laboratory, National Institutes of Allergy and Infectious Disease, Hamilton, Mont.

[3] National Institutes of Health, Public Health Service, U.S. Department of Health, Education, and Welfare.

die about 60 days after intradermal inoculation of 1.5×10^6 tumor cells (*2*).

Preparation of BCG cell walls.—Cell walls of the Glaxo strain of BCG were prepared as in (*10*). Mycobacteria were grown in Sauton's medium at the Lederle Laboratories (Pearl River, N.Y.). After 3 weeks in culture, the bacteria were disrupted in the Sorvall refrigerated pressure cell at 35,000 pounds per square inch. Cell walls were obtained by centrifugation of the mixture at 20,000 × *g* for 1 hour. The pellet was resuspended in distilled water and washed several times until only cell walls were visible under the electron microscope.

Preparation of BCG cell walls attached to oil droplets.—Freeze-dried cell walls (25 mg) were placed in a 15-ml tissue grinder equipped with a Teflon pestle (Scientific Glass Apparatus Co., Inc., Bloomfield, N.J.). A light mineral oil (0.12 ml), Drakeol 6 VR (Pennsylvania Refining Co., Butler, Penna.), was added to the cell walls. This mixture was ground to a smooth paste; the pestle was rotated at 800 rpm. Ten ml 0.85% NaCl containing 0.2% Tween 80 (polyoxyethylene derivative of sorbitan mono-oleate, Atlas Powder Co., Wilmington, Del.) was added to the paste, and grinding was continued until a well-dispersed oil-in-water emulsion was obtained. The emulsion was poured into a sterile container and 6.7 ml Tween-saline diluent was added to the grinding tube. Grinding was continued for 2–3 minutes. The 2 emulsions were combined and ground for an additional 2–3 minutes. This emulsion containing 1.5 mg cell walls per ml was heated at 65°C for 30 minutes in a water bath. Examination of the product with the light microscope showed spherical oil droplets varying from $<1\ \mu$ to $>15\ \mu$; discrete particles appeared to be attached to the surface of the oil droplets. Photographs of similar emulsions are in (*11*).

Preparation of oil droplets alone, cell walls alone, and cell walls not attached to oil droplets.—Oil droplets alone: This preparation was made in the same way as the BCG cell walls attached to oil droplets except for the omission of the cell walls. Under the light microscope this product showed clear spherical oil droplets varying from $<1\ \mu$ to $>15\ \mu$. Cell walls alone: The method was the same as for the BCG cell walls attached to oil droplets except for the omission of the oil. Under the light microscope this product showed cell wall fragments varying from 2–5 μ. Cell walls not attached to oil droplets: In this preparation, the oil in water emulsion was made first and the cell walls were added without further grinding. The cell walls were dispersed in the emulsion by gentle mixing. Under the light microscope this product showed clear spherical oil droplets of varying size and aggregated cell walls that remained unattached to oil droplets.

Preparation of tumor cell mixtures for inoculation.—Ascites tumor cells, obtained as described in (*12*), were washed 3 times in medium 199 without antibiotics. Equal volumes of ascites tumor cells and the appropriate emulsion or cell wall preparation were mixed at room temperature in 13 × 100 mm siliconized, sterile, glass test tubes; they were incubated at 37°C for 10 minutes, and then 0.1 ml was injected intradermally into unimmunized guinea pigs.

Measurement of delayed skin reactions and papules.—Delayed skin reactions were measured 24 hours after injection of the mixtures. Papules were measured at several intervals after injection. Two diameters of the skin reaction or papule perpendicular to one another were measured. The two diameters were used to calculate the square of the average radius of the skin reaction or papule. In experiments in which several animals were challenged with portions of the same tumor-cell mycobacterial antigen mixture, the square of the average radius for each lesion produced by the same number of tumor cells was calculated. Results were expressed as the mean of the square ± the standard error of the mean.

Each experimental group contained 3 guinea pigs. At each time point, the results represent the mean value of 3 animals. Each animal received a single test mixture.

RESULTS

In preliminary experiments, oil-treated cell walls of BCG were injected intradermally into guinea pigs immunized with BCG and into unimmunized guinea pigs. The following day, typical delayed cutaneous-hypersensitivity reactions were seen only in guinea pigs immunized to BCG. Three days later, in immunized and unimmunized guinea pigs an inflammatory nodule was at the injection site of

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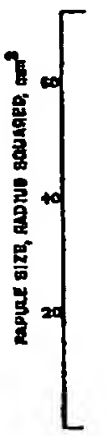

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oil-treated cell walls of BCG. This nodule persisted for 3 weeks. A small scar was left at the site of the healed nodule. This experiment indicated that oil-treated cell walls of BCG contained mycobacterial antigens and, like living BCG, produced a chronic inflammatory nodule which healed in 3–4 weeks.

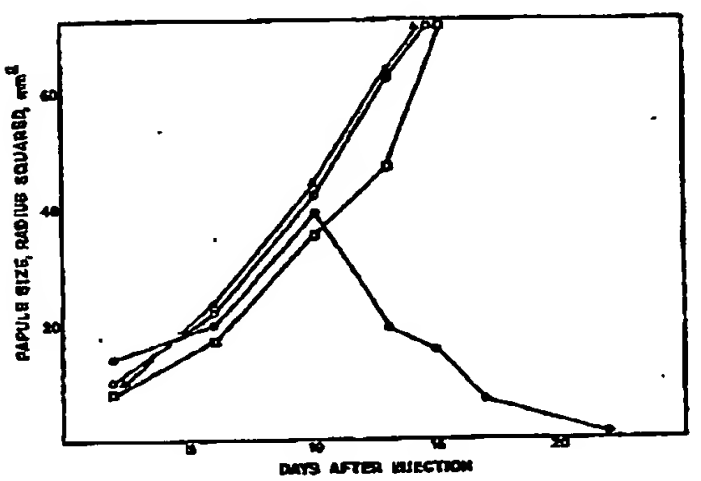
The possible tumor-suppressive properties of oil-treated cell walls were evaluated in the next experiment. Group 1 received an intradermal injection containing oil-treated cell walls (75 μg) and 1.5×10^6 living line-10 tumor cells. Group 2 was given an intradermal injection containing oil droplets without cell walls and 1.5×10^6 living line-10 tumor cells. Group 3 received an intradermal injection containing 1.5×10^6 living line-10 cells diluted with 0.85% saline containing 0.2% Tween. Group 4 was inoculated intradermally with 1.5×10^6 living line-10 tumor cells diluted with 0.85% saline without Tween. The results of the experiment are illustrated in text-figure 1. Oil-treated cell walls completely suppressed tumor growth. Oil droplets without cell walls or saline containing Tween did not inhibit tumor growth.

The following experiment was designed to determine whether bacterial cell walls without oil droplets would inhibit tumor growth and whether the cell walls had to be attached to the oil droplets for tumors to be suppressed. Group 1 received an intradermal injection of 75 μg oil-treated cell walls + 1.5×10^6 living line-10 tumor cells. Group 2 was given 75 μg cell walls without oil droplets + 1.5×10^6 living line-10 tumor cells. Group 3 received 75 μg cell walls not attached to oil droplets + 1.5×10^6 line-10 cells. Group 4 was treated with 1.5×10^6 line-10 cells diluted with saline containing Tween. The results of this experiment (text-fig. 2) indicate that cell walls alone and cell walls in the presence of, but not attached to, oil droplets were ineffective in tumor inhibition.

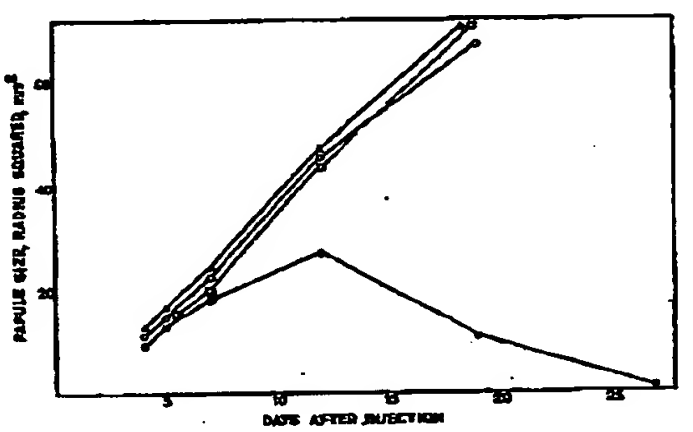
To test whether guinea pigs treated with a mixture of oil-treated cell walls of BCG and tumor cells had developed systemic tumor immunity, guinea pigs received intradermal injections of 10^6 living line-10 tumor cells. The challenge dose was inoculated contralateral to the immunization site. The presence of delayed cutaneous hypersensitivity reactions to tumor cells and prevention of tumor growth (table 1) indicate that guinea pigs treated with vaccine had developed systemic tumor immunity.

DISCUSSION

These experiments demonstrate that a nonliving mycobacterial preparation can completely suppress tumor growth. The tumor-suppressive property of oil-treated cell walls is in contrast to the previously



TEXT-FIGURE 1.—Suppression of tumor growth by oil-treated cell wall of BCG. ●: Cell walls attached to oil droplets + 1.5×10^6 line-10 tumor cells. O: Oil droplets + 1.5×10^6 line-10 tumor cells. □: 0.85% saline containing 0.2% Tween 80 + 1.5×10^6 line-10 tumor cells. △: 0.85% saline + 1.5×10^6 line-10 tumor cells



TEXT-FIGURE 2.—Suppression of tumor growth by oil-treated cell walls of BCG. ●: Cell walls attached to oil droplets + 1.5×10^6 line-10 tumor cells. O: Cell walls + 1.5×10^6 line-10 tumor cells. □: 0.85% saline containing 0.2% Tween 80 + 1.5×10^6 line-10 tumor cells. △: Cell walls not attached to oil droplets + 1.5×10^6 line-10 tumor cells.

TABLE 1.—Tumor immunity after intradermal injection of oil-treated mycobacterial cell walls and living tumor cells

Treatment	Delayed cutaneous hypersensitivity reactions at 24 hr—radius squared, mm²		Tumor incidence at 10 days after challenge with 10^6 tumor cells	
	Expt. 1*	Expt. 2	Expt. 1	Expt. 2
Oil-treated cell walls and living tumor cells	27 ± 2	Not done	0/3	0/3
None	7 ± 1	Not done	6/6	5/5

*In expt. 1, guinea pigs were challenged the 28th day after immunization and in expt. 2 the 22d day after immunization. Immunized animals were free of tumor at the time of this report, 2 months after challenge. Tumors in the unimmunized group grew progressively.

reported (*2*, *13*) lack of tumor inhibition in guinea pigs not immunized to BCG when other nonliving mycobacterial antigen preparations were used (cell walls alone, purified protein derivative, heat-killed BCG, crude tuberculoprotein). In immunized guinea pigs, tumor may be partially suppressed by these nonliving antigens. There have been reports that nonliving preparations or fractions of mycobacteria are effective in tumor inhibition (*14*). The experimental model described in this report offers the possibility of comparing the tumor-inhibiting capacity of nonliving preparations of mycobacteria.

Injection of oil-treated cell walls mixed with living tumor cells leads to the development of tumor immunity. Recent studies of tumor immunity produced by injection of mycobacterial antigen-tumor cell mixtures indicate that differences exist in the intensity of tumor immunity produced by different mycobacterial antigen preparations (*15*). For example, intradermal immunization with complete Freund's adjuvant and tumor cells was not as effective as intradermal immunization with living BCG and tumor cells.

We do not know why BCG cell walls attached to oil droplets can suppress tumor growth. If the mechanism of tumor suppression by oil-treated BCG cell walls is similar to that obtained with living BCG, this means that in some unknown fashion the oil droplets make it possible for the recipient to respond immunologically to BCG cell-wall antigens by the production of specifically sensitized lymphocytes. Interaction of these lymphocytes and BCG antigens in the presence of tumor cells causes the accumulation of nonlymphoid cells responsible for tumor cell death.

This work may provide a simple, rapid model for determining the components of the tubercle bacillus required for tumor suppression and indicates that a nonliving mycobacterial antigen preparation may be clinically useful for inhibiting tumor growth.

REFERENCES

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(*2*) ZBAR B, BERNSTEIN ID, RAPP HJ: Suppression of tumor growth at the site of infection with living bacillus Calmette-Guérin. J Nat Cancer Inst 46:831–839, 1971

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(*8*) ZBAR B, WEPSIC HT, RAPP HJ, et al: Antigenic specificity of hepatomas induced in strain-2 guinea pigs by diethylnitrosamine. J Nat Cancer Inst 43:833–841, 1969

(*9*) ZBAR B, WEPSIC HT, RAPP HJ, et al: Transplantable hepatomas induced in strain-2 guinea pigs by diethylnitrosamine: Characterization by histology, growth, and chromosomes. J Nat Cancer Inst 43:821–831, 1969

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